Biological Model for Predicting Toxicity in Head and Neck Cancer Patients Receiving Proton Therapy

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Abstract

Purpose: To use a linear energy transfer (LET) dependent formula for relative biological effectiveness (RBE) to generate a biological model that can be used to predict toxicity in patients treated with proton therapy for cancer of the head and neck.

Patients and Methods: Patients treated with protons to a dose of 60 to 70 Gy (RBE = 1.1) for head and neck cancer were eligible to participate in this study. Treatment plans were developed using graphics processing unit Monte Carlo calculations. The equation, $RBE = (1.1)[0.08(LET_d)+0.88]$, was the biological model. The physical model assumes RBE = 1.1. Tumor volumes and organs at risk (OARs) were contoured, and isodose lines were created for 105%–120% of the prescribed dose. Dose to volume of OARs was calculated for both models for comparative purposes. Physician-reported toxicity was graded from 0 to 5 using the Common Terminology Criteria for Adverse Events, version 4.03. Patient-reported outcomes were obtained using the Promis10 and European Organisation for Research and Treatment of Cancer's QLQ-H&N35 instruments.

Results: Eleven patients were included in this study. In each case the biological model revealed an increased dose to several OARs compared with the physical model. For selected OARs, the volume receiving >105% of the target dose was 2-fold to 15-fold greater in the biological model than the volume predicted by the physical model. Patients experienced toxicity that was consistent with the dose to OARs predicted by the biological model. Furthermore, 1 patient developed mucosal ulceration and another developed osteoradionecrosis at the location of a biological hot spot. In each case, the biological hot spot was located 2 mm inside the clinical target volume.

Conclusion: The results suggest that increases in dose predicted by the biological model are clinically relevant and that LET and RBE corrections and optimization should be a component of the treatment-planning process in proton therapy.

Keywords: head and neck cancer; organ at risk; osteoradionecrosis; proton therapy; relative biological effectiveness

Introduction

The physical properties of protons allow for a more targeted delivery of radiation to the treatment volume with decreased dose to surrounding structures. This is especially important in the head and neck, where cancers are often encroaching on critical healthy organs. A review of evidence for the use of proton therapy for selected subsites (base of

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skull, nasal cavity, paranasal sinus, nasopharynx, oropharynx, periocular, parotid, and skin) suggests that it is superior to photons in reducing toxicity without compromising local tumor control [1]. A recent MD Anderson Cancer Center series compared intensity-modulated proton therapy (IMPT) to intensity-modulated radiation therapy using photons for nasopharyngeal cancer and found a 3-fold reduction in the rate of gastrostomy tube placement for patients receiving protons, which was attributed to decreased oral cavity toxicity [2]. Additional studies evaluating the use of protons in head and neck cancer have yielded similar conclusions [3–6].

Relative biological effectiveness (RBE) is the ratio of the proton dose to photon dose for a given biological effect. Protons are thought to be 10% more effective than photons and are thus assumed to have a RBE of 1.1. This assumption ignores experimental data that suggest that RBE varies with respect to tissue type (ie, α/β), dose per fraction, and linear energy transfer (LET) [7]. In fact, RBE may approach 1.3 at the distal edge of the spread-out Bragg peak and 1.7 in the fall off region [8]. In addition, RBE varies based on biologic endpoint measured as shown in a recent analysis of 70 reports by Paganetti [8]. The data from this analysis were extracted and used to generate a comprehensive biological model for cell survival [9]. This model is consistent with other models in the literature using more limited data sets [10, 11].

The physical dose is well modeled in proton therapy using Monte Carlo (MC) techniques. However, biological dose uncertainty is a barrier to treatment optimization. Notably, underestimating RBE could result in a higher than anticipated biologic dose to critical structures and an underestimation of normal tissue complication probabilities. The process of IMPT uses beams that deliver inhomogeneous LET distributions, and hot spots may be present within critical structures in or near the target volume. To reduce the likelihood of complications we have developed an equation for RBE that is consistent with equations in the literature [9–11]. In the present study, the authors compared a biological model generated from their RBE equation with a physical model that assumes that RBE $= 1.1$ for 11 patients treated with proton beam therapy for head and neck cancer.

Materials and Methods

Dose Calculation

Initial treatment plans were optimized using the Eclipse treatment-planning system (Varian Medical Systems, Palo Alto, California). Plans were then recalculated using graphics processing unit MC calculations [12, 13].

The MC calculations were also used to calculate dose-averaged LET (LET_d). Although the relationship between LET_d and RBE is difficult to know, a linear form for LET_d between 1 and 10 keV/μm was assumed (**Figure 1**). The linear model used here was $RBE = (1.1)[0.08(LET_d) + 0.88]$ [14, 15]

Of important note is that we are not claiming that the RBE of protons follows this equation; rather, implementation of this equation aids in detection of possible areas of high biologic dose at risk for complications. Fractionation, both number of fractions and dose per fraction, is explicitly excluded from this formula. This model agrees well with other published models for α/β values of 2.0 ± 1.0 and a dose of 2 Gy per fraction [9–11]. The constant values were chosen to give an RBE of 1.5 for a LET_d of 6.0 keV/μm and 1.1 for a LET_d of 1.5 keV/μm.

Plan Evaluations

Patients treated with pencil beam scanning IMPT to a dose of 60 to 70 Gy (RBE $= 1.1$) for cancer of the head and neck were eligible for participation. Institutional review board approval was obtained and all patients provided written consent. The first 11 consecutive patients with plans available for research purposes were included. The gross tumor volume, clinical target volume (CTV), and organs at risk (OARs) for complications were contoured on a simulation computed tomography scan prior to exporting the images to the treatment-planning system. Specific OARs were brain, brain stem, spinal cord, optic nerve, optic chiasm, eyes, nasal cavity, oral cavity, lips, mandible, parotid glands, submandibular glands, cochlea, semicircular canals, pharyngeal constrictor muscles, submandibular glands, larynx, thyroid gland, esophagus, and brachial plexus. Selected OAR contours were drawn to avoid overlapping the CTV (ie, the OARs were excluded from the CTV for nasal cavity, oral cavity, and lips). After calculating and optimizing treatment plans in the Eclipse treatment-planning system, each patient had his or her simulation computed tomography scan, structure set, physical dose, and biologic dose anonymized and exported to a research treatment-planning system that matched the clinical treatment-planning system.

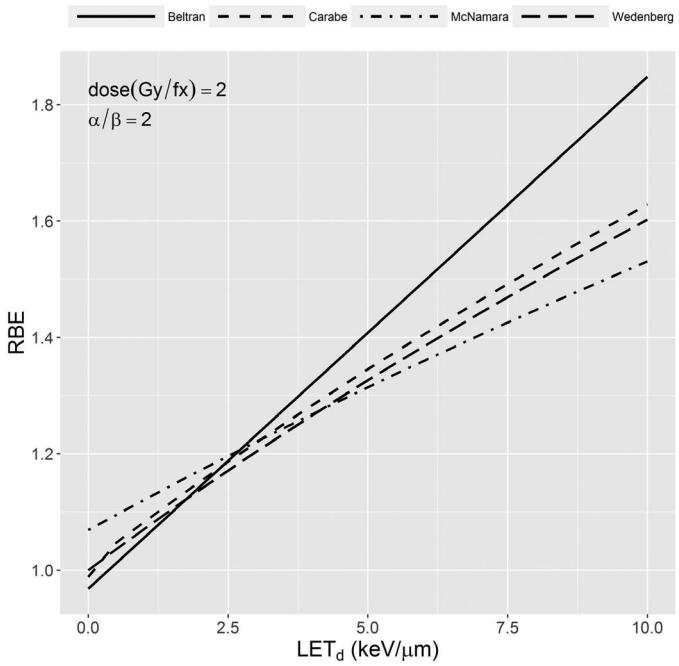


Figure 1. The present dose-averaged linear energy transfer-dependent formula for relative biological effectiveness (Beltran et al [14]) compared with previously developed models (Carabe et al [10], McNamara et al [9], Wedenberg et al [11]).

Isodose lines from the biological and physical plans were converted to contours at 105%, 110%, 115%, and 120% of the prescribed dose. The volume of the OARs outside the CTV receiving a dose greater than the prescribed dose was calculated. Areas of potential high biologic dose within an OAR contained within the CTV were also noted.

Toxicity

Physician-reported toxicity was graded from 0 to 5 using Common Terminology Criteria for Adverse Events, version 4.03. Patient-reported outcomes were obtained using the Promis10 and European Organisation for Research and Treatment of Cancer's QLQ-H&N35 instruments. Toxicity attributed to proton therapy was assessed at the following time intervals: posttreatment (11 days before the last day of treatment to 16 days after last day of treatment), 3 months (17 to 136 days after the last day of treatment), 6 months (between 137 and 274 days after the last day of treatment), and 12 months (between 275 and 547 days after the last day of treatment). Toxicity outcomes were not known at the time the biological and physical plans were compared. In cases of severe and localized unanticipated toxicity, plans were reviewed a second time to check for correlating high biological dose volumes to the location of unexpected toxicity.

Dose Nomenclature

For the remainder of this article, Gy (RBE = 1.1) will imply dose according to the physical model and Gy (RBE eq) will refer to dose according to the biological model.

Results

Patients

Ten patients had squamous cell carcinoma arising from the oropharynx (n = 5), nasopharynx (n = 2), oral cavity (n = 1), external auditory canal (n = 1), and skin (n = 1). One patient was treated for multiply recurrent ameloblastoma of the maxilla. Six patients had received prior radiation therapy. All patients were treated with IMPT to a dose of 60 to 70 Gy (RBE = 1.1).

Plan Evaluations

Compared with the physical model, the biological model predicted a higher dose within several localized regions. Affected OARs included the oral cavity, mandible, pharyngeal constrictor muscles, parotid gland, and brain. In all 11 cases, the CTV was directly adjacent to at least 1 OAR. For selected OARs, the volume receiving >105% of the prescribed dose was 2-fold to

Table 1. Physical vs biological model dose comparison.

Patient	Tumor location	Dose (Gy [RBE])	Organ at risk	Model	Volume receiving dose >100% prescribed (cm^3)			
					105%	110%	115%	120%
1	Tonsil	60	Oral cavity	Biological	2.9	2	1.4	0.8
				Physical	0.1	0	0	0
2	Maxillary sinus	66	Oral cavity	Biological	2.7	0.5	0	0
				Physical	0	0	0	0
			Right parotid gland	Biological	2.9	1.1	0	0
				Physical	0	0	0	0
3	Skin	66	Temporal lobe	Biological	42.8	23.2	8.4	2.3
				Physical	5.7	2.1	<0.1	0
4	Tonsil	70	Pharyngeal constrictors	Biological	4.9	4	2	0.4
				Physical	0.1	<0.1	0	0
5	External auditory canal	60	Mandible	Biological	4.1	3	0.8	0.1
				Physical	<0.1	0	0	0
6	Tonsil	70	Pharyngeal constrictors	Biological	3.4	0.07	0	0
				Physical	0	0	0	0
			Left parotid gland	Biological	4.8	2.1	0	0
				Physical	0.5	0	0	0
7	Nasopharynx	70	Temporal lobe	Biological	15.2	4.8	0.1	<0.1
				Physical	<0.1	0	0	0
8	Tonsil	70	Pharyngeal constrictors	Biological	5.6	3.3	0	0
				Physical	2.7	0	0	0
			Right parotid gland	Biological	7.9	4.8	0	0
				Physical	3.4	0	0	0
9	Nasopharynx	70	Oral cavity	Biological	3.3	1.1	0	0
				Physical	1	0.9	0	0
10	Oral cavity	60	Mandible	Biological	8.6	2	0.2	<0.1
				Physical	0.1	0	0	0
11	Tonsil	66	Left parotid gland	Biological	1.8	<0.1	0	0
				Physical	0	0	0	0

15-fold greater in the biological model than the volume predicted by the physical model (**Table 1**). Additionally, biological hot spots were identified within an OAR in 3 patients and at the border of the OAR and CTV in 8 patients.

Toxicity

Episodes of acute and late toxicity attributed to proton beam therapy are summarized in **Table 2**. There were no grade 4 or 5 toxicities at any time point. Patients with prior radiation therapy did not experience an overall increase in toxicity compared with patients who were treated with radiation for the first time.

Immediate posttreatment toxicity was recorded for all 11 patients. The most common posttreatment grade 1 toxicities were skin pain (n = 3) and weight loss (n = 3). The most frequent grade 2 toxicities were fatigue (n = 7), pharyngolaryngeal pain (n = 4), and dry mouth (n = 4). Seven patients experienced grade 3 dermatitis.

Three-month toxicity was known for all 11 patients. The most common grade 1 toxicities were dry mouth (n = 7), dermatitis (n = 4), salivary duct inflammation (n = 4), and trismus (n = 4). The most common grade 2 toxicities were fatigue (n = 6) and weight loss (n = 3). Grade 3 toxicities included oral pain (n = 2), weight loss (n = 2), oral mucositis (n = 1), and pharyngolaryngeal pain (n = 1).

Six-month toxicity was known for 6 patients. The most common grade 1 toxicities were dry mouth (n = 4) and dysgeusia (n = 2). Three patients had grade 2 fatigue. There was no grade 3 toxicity at 6 months.

Twelve-month toxicity was known for 5 patients. The most common grade 1 toxicities were dry mouth (n = 3) and dysgeusia (n = 2). Grade 2 toxicities included oral pain (n = 1), pharyngolaryngeal pain (n = 1), and trismus (n = 1).

Table 2. Specific toxicity attributed to current proton treatment. N represents the number of distinct patients for which there is follow-up at each time point. The values in the table are the number of patients that had a radiation attributed side effect of grade 1 or higher at the given time (posttreatment, 3 months, 6 months, 12 months).

	No. of patients with toxicity attributed to proton treatment											
	Posttreatment (n = 11)			3 month (n = 11)			6 month (n = 6)			12 month (n = 5)		
Toxicity	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Dermatitis radiation	1	3	7	4	-	-	-	-	-	1	-	-
Dry mouth	1	4	-	7	2	-	4	-	-	3	-	-
Dysgeusia	-	2	-	3	1	-	2	-	-	2	-	-
Fatigue	2	7	-	3	6	-	-	3	-	1	-	-
Mucosal infection		3	-		-	-	-	-	-	-	-	-
Mucositis oral	1	3	-	1	-	1	-	-	-	-	-	-
Oral pain	1	3	-	1	1	2	1	-	-	-	1	-
Pain of skin	3	3	-	-	1	-	-	-	-	-	-	-
Pharyngolaryngeal pain	-	4	-	-	1	1	-	-	-	-	1	-
Salivary duct inflammation	1	3	-	4	1	-	1	-	-	-	1	-
Trismus	1	1	-	4	-	-	1	1	-	1	-	-
Weight loss	3	2	-	2	3	2	1	1	-	-	-	1
Grand total	6	11	7	10	7	3	4	3	-	4	2	1

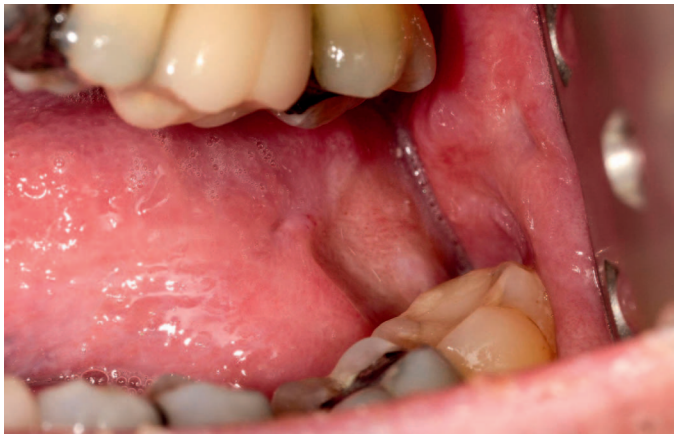
Mucosal Ulceration

One patient developed a painful ulceration (grade 3) of the mucosa involving the left posterior tongue during treatment that was still present 19 weeks after completion of treatment (**Figure 2**). This patient was treated to 66 Gy (RBE = 1.1) in 30 fractions for recurrent tonsillar cancer that was originally treated with surgery alone. The ulcer developed 2 mm inside of the CTV-66 Gy in an area where the biological dose was predicted to be approximately 76 Gy (RBE eq) (**Figure 3**). According to the physical model, this area was receiving 69 Gy (RBE = 1.1). The ulcer had healed completely by 7 months following completion of treatment.

Osteoradionecrosis

Another patient developed osteoradionecrosis (grade 3) adjacent to tooth No. 27 in the right mandible, which required surgical debridement. This patient had been treated with adjuvant radiation to 60 Gy (RBE = 1.1) in 30 fractions for an oral cavity gingival cancer following partial mandibulectomy with the osteotomy adjacent to tooth #27. The osteoradionecrosis developed in an area where the biological dose was predicted to be approximately 77 Gy (RBE eq) 2 mm within the medial border of the CTV-60 Gy (**Figure 4**). According to the physical model this area received 63 Gy (RBE = 1.1).

Figure 2. Mucosal ulceration at left posterior tongue at 19 weeks following completion of proton treatment.



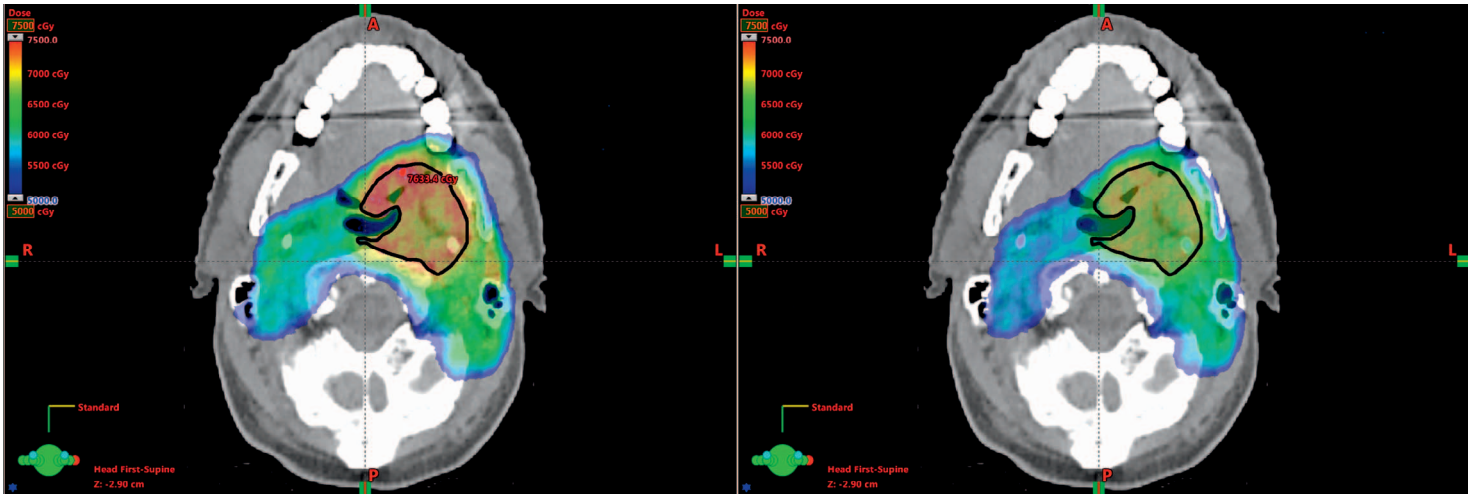


Figure 3. Comparison of the biological plan (left) and physical plan (right) for a patient who developed a grade 3 painful ulcer in the left posterior tongue adjacent to the mandibular last molar. Dose is shown in colorwash (limits 50 to 75 Gy relative biological effectiveness [RBE]). Clinical target volume (CTV)-66 Gy is outlined by the black line. The hot spot (~76 Gy [RBE eq]) is indicated by a red dot in the biological model and is 2 mm from the anterior border of the CTV-66 Gy. The dose in this area according to the physical model is 69 Gy (RBE = 1.1).

Discussion

Outcomes following proton therapy can be improved by methods that more accurately predict biologic dose to the target volume and surrounding OARs. The aim of this study was to use an equation for RBE to construct a biological model that, when compared with a physical model, could identify areas of potential toxicity and inform treatment planning.

In each of the 11 plan comparisons, the biological model identified areas of potential toxicity that were not identifiable in the physical model. The clinical significance of these dose prediction differences was dependent on number of beams and beam arrangement. For the biological model, the correlation among areas of higher LET and RBE and toxicity was dependent on the anatomical location of the CTV and OARs. Common areas where the biological model predicted an increased dose included the oral cavity, pharyngeal constrictor muscles, and salivary glands. This is not surprising considering that many target volumes extended into or near these OARs, placing them at the distal edge of the spread-out Bragg peak where RBE has

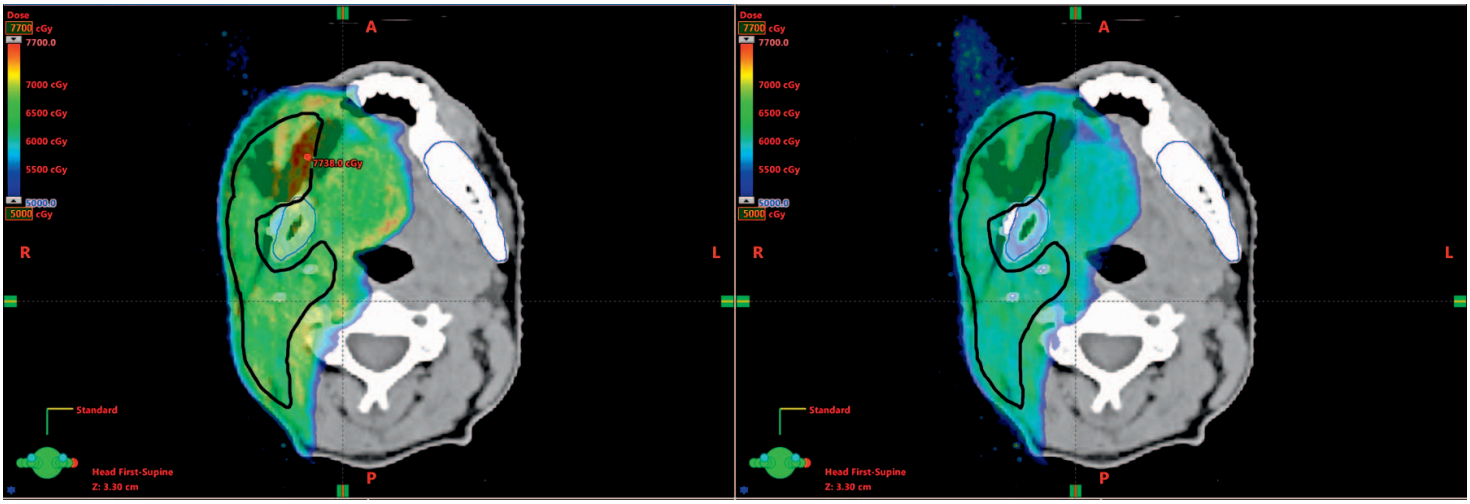


Figure 4. Comparison of the biological plan (left) and physical plan (right) for a patient who developed bone exposure/osteoradionecrosis adjacent to the last tooth in the right mandible at the anterior end of the reconstructed mandible. Dose is shown in colorwash (limits 50 to 77 Gy relative biological effectiveness [RBE]). Clinical target volume (CTV)-60 Gy is outlined by the green line, and the mandible is contoured in blue. The hot spot (~77 Gy [RBE eq]) is indicated by the red dot in the biological model 2 mm within the medial border of the CTV-66Gy. The dose in this area according to the physical model is ~66 Gy (RBE = 1.1).

been shown to be as high as 1.7 [7]. This was done to avoid putting the distal edge of the spread-out Bragg peak and area of high RBE in the brain stem, spinal cord, or mandible. The correlation between higher LET and RBE and toxicity in the oral cavity and oropharynx was strong. For higher LET and RBE in regions such as the brain or mandible, the correlation was not as strong. Higher LET and RBE did not always result in unwanted toxicities. These initial observations should be considered exploratory and used to support more detailed studies in a larger cohort of patients with longer follow-up to determine the magnitude of the correlation between higher LET and RBE and toxicity.

Biological hot spots were noted in each plan comparison, and in many cases the biological and physical models revealed hot spots occurring at different locations. For 2 patients, the biological hot spot was proven to be clinically relevant as the patients experienced unexpected severe toxicity at the exact location predicted to be a hot spot according to the biological model.

Previous work has investigated IMPT optimization based on biological dose, although such approaches have not yet been adopted clinically due in part to concern for underdosage in the target volume if RBE is overestimated. More recently, Unkelbach et al [16] have introduced a method to avoid high values of LET in critical structures near the target volume in patients treated with IMPT for intracranial tumors. After an IMPT plan based on a physical model is generated, a graphics processing unit based MC code is added to provide LET_d, and the product of LET_d and physical dose is used to optimize the dose distribution. Using this method the authors were successful in avoiding biological hot spots in serial critical structures such as the brain stem and optic nerve.

The present approach considers a MC-based physical plan and a biological plan in which MC is used to calculate LET_d. By using both plans, we mitigate the limitations of each when used exclusively, namely, ignoring LET variation in the physical plan and the uncertainty of RBE in the biological plan. Of the 11 patients, 2 were found to have unexpected severe toxicity at the exact location of a hot spot suggested by the biological model, which supports further investigation of the use of the biological model to inform treatment.

The LET is modeled accurately using available MC codes. Thus, the uncertainty in dose using protons is due to the uncertainty in RBE. Use of IMPT is improved by multi-field optimization and LET-based optimizations that spread the higher LET over the target. We strongly recommend using LET and RBE corrections and optimization to improve biologic dose estimates and distribution.

Conclusion

The authors suggest that increases in dose predicted by LET and RBE corrections are clinically relevant and should be a component of the treatment-planning process in proton therapy.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflicts of Interest: The authors have no conflicts to disclose.

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